UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/731,467	12/07/2000	Charles Jack Fisher	X-12448A	6830

25885 7590 04/09/2002

ELI LILLY AND COMPANY
PATENT DIVISION
P.O. BOX 6288
INDIANAPOLIS, IN 46206-6288

EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	2

DATE MAILED: 04/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/731,467	Applicant(s) FISHER ET AL.	
	Examiner Manjunath N Rao	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-20 are now pending and present for examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glas-Greenwalt et al. (J. Lab Clin. Med., 1986, Vol. 108:415-422) Gruber et al. (Circulation, 1990, Vol. 82:578-585), Foster et al. (US 5,516,650, 5-14-1996) . Claims 1-5 in this instant application are drawn to a method of treating a patient suffering from thrombotic thrombocytopenic purpura (TTP) comprising the administration of a pharmaceutically effective amount of protein C (PC) wherein the PC is human zymogen, human activated PC and wherein the amount of activated PC is about 1-96 microgram/kg/hr and wherein the activated PC is administered by continuous infusion for about 1 to 240 hours.

Glas-Greenwalt et al. teach the characteristics of TTP disorder in terms of blood bio-chemistry and physiology with respect to plasma fibrinolysis and PC. The reference teaches that PC levels were low in three of the six patients studied. While discussing elaborately the consequences of the TTP disorder, the above reference also teaches that plasma exchange (wherein plasma containing nascent or activated PC was obtained from non-effected individuals) resulted in temporary reversal of the abnormalities. The reference also teaches that it is possible that a defect in the fibrin-clearing system permits thrombus formation to occur and proceed in an unchallenged fashion thereby contributing to the complex events leading to arterial

ischemia in vital organs. However, the reference does not teach recombinant human protein C or its use in treatment of TTP.

Gruber et al. teach the inhibition of thrombus formation which is very similar to conditions of TTP (a platelet dependent thrombosis) by activated human recombinant protein C in a primate model of arterial thrombosis using baboons as model. The reference also teaches the methods of administering recombinant protein C in a pharmaceutical composition as a continuous infusion at a specific dosage. The reference also teaches that recombinant human activated protein C, like the human plasma derived PC or plasma-derived activated protein C inhibited the thrombus formation. While the reference does not teach the same dosage levels as that in the instant invention, it however gives the dosages used in the experiments using primates that are close relatives of humans. The reference teaches that the doses tried in the experiment significantly inhibited fibrin deposition in the graft and that circulating plasma markers of thrombus formation and fibrinolysis did not increase significantly during the infusion and that measurements of bleeding time were also within normal limits.

Foster et al. teach methods of producing PC and activated PC wherein the protein has substantially the same biological activity as human PC or human activated PC. The reference teaches the production of the protein using mammalian host cells transfected with a plasmid capable of integration in mammalian host cell DNA. The reference also teaches that while PC may be purified from clotting factor concentrates or from plasma and activated in vitro, it is a complex and expensive process, in part due to the limited availability of the starting material and low concentration of PC in plasma. Furthermore, the therapeutic use of products derived from human blood carries the risk of disease transmission by viruses. The reference teaches that it is preferable to produce PC and activated PC by recombinant methods and provides methods for the same.

Thus, from the above three references and their review it appears that TTP (as well as HUS) are basically conditions that arise due to the formation of thrombi in peripheral arterioles leading to widespread occlusion of blood vessels. It also appears that fibrinolysis components such as protein C and t-PA are mainly anti-thrombotic in function. Apart from the function of being anti-thrombotic, protein C also appears to have other properties such as increasing the activity of t-PA. It also appears that the TTP disorder was well studied by those skilled in the art in great detail and that the same disorder has been coined different names in the art. It also appears that there were treatment methods being developed for the same such as plasma exchange therapy or the use of recombinantly made PC (see Gruber et al. and Foster et al.). Armed with the above references it would have been obvious to one skilled in the art at the time the invention was made to combine the teachings of Glas-Greenwalt et al. with that of Gruber et al. and Foster et al. to develop a method of treatment for TTP using recombinant human PC. Gruber et al. and Foster et al. teach that one would be motivated to do this in order to develop and use PC as antithrombotic agent to treat septic shock and stroke which are final manifestations of TTP and provide the methods and agents (recombinant PC and activated recombinant PC) for the same. Gruber et al. actually teach an experiment using primates with highly encouraging results that would motivate one of ordinary skill in the art to extend the same to humans with appropriate dosage and infusion methods. One of ordinary skill in the art would also be motivated to develop and use a recombinant PC as natural protein C is manufactured from donated blood plasma which is usually in short supply and also to avoid contamination of the final protein C product with potential bacterial or viral pathogens. One of ordinary skill in the art would have a reasonable expectation of success since Glas-Greenwalt et al. teach that PC antigen levels were low in TTP patients and that plasma (normal plasma) exchange therapy resulted in temporary reversal of TTP abnormalities and Gruber et al. teach that recombinant activated PC, like human plasma derived activated PC, inhibited thrombus

formation in a primate model clinical trial. Finally, Foster et al. teach a reliable and time-tested method for making recombinant human PC and activated PC.

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have performed the claimed invention.

Claims 6-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glas-Greenwalt et al. (J. Lab Clin. Med., 1986, Vol. 108:415-422) Gruber et al. (Circulation, 1990, Vol. 82:578-585), Foster et al. (US 5,516,650, 5-14-1996) as applied to claims 1-5 above, and further in view of Hollenbeck et al. (Nephrol. Dial. Transplant., 1998, Vol. 13:76-81). Claims 6-20 are drawn to a method of treatment of TTP and hemolytic uremic syndrome (HUS) conditions comprising administering a pharmaceutically effective amount of PC or activated PC wherein the amount of human activated PC is about 1-96 microgram/kg/hr, such that the plasma levels of activated PC range between 2 ng/ml to about 300 ng/ml achieved in 1 to 240 hours wherein the PC is administered either as a bolus injection or as a continuous infusion or wherein one third of the activated PC required is administered in a bolus injection followed by continuous infusion of the remaining two-thirds of the required activated PC (claims 6-10); and to a method of treating a patient with hemolytic uremic syndrome (HUS) conditions comprising administering a pharmaceutically effective amount of human PC or activated PC wherein the amount of human activated PC is about 1-96 microgram/kg/hr, such that the plasma levels of activated PC range between 2 ng/ml to about 300 ng/ml achieved in 1 to 240 hours wherein the PC is administered either as a bolus injection or as a continuous infusion or wherein one third of the activated PC required is administered in a bolus injection followed by continuous infusion of the remaining two-thirds of the required activated PC (claims 11-20).

Glas-Greenwalt et al., Gruber et al. and Foster et al. were discussed above as applied to claims 1-5 which is overall very similar to claims 6-20. However, the above references do not

teach methods for using PC or activated PC to treat hemolytic uremic syndrome (HUS). Hollenbeck et al. teach that both TTP and HUS are characterized by similar outcomes such as microangiopathic hemolytic anemia, thromobocytopenia, and functional impairment of various organs and that there is considerable overlap between the clinical pictures and morphological findings of both disorders the two syndromes are now increasingly referred to HUS-TTP. The reference also teaches that case reports and more recent prospective studies indicate that the prognosis is favorably influenced by therapy with plasma exchange. It is also well known in the art that plasma is source of protein C and activated protein C.

Thus, it would have been obvious to one skilled in the art to combine the teachings of Glas-Greenwalt et al. , Foster et al. and Gruber et al. with that of Hollenbeck et al. and develop a method of either treating both TTP and HUS disorders or just the HUS disorder, which normally occurs in individuals with transplanted organs such as kidneys, using recombinant human PC and recombinant activated human PC. While Hollenbeck et al. does not provide any dosages or methods of infusion for humans, based on the experiments of Gruber et al. using primates, it would be obvious to one of ordinary skill in the art to empirically set up dosages, safe methods of infusion and time required for such infusions. One of ordinary skill in the art would have been motivated to do so as two closely related abnormalities such as TTP and HUS can be treated with a single agent such as human PC or activated PC. One of ordinary skill in the art would have had a reasonable expectation of success, since Gruber et. al. show promising results from primate experiments and Hollenbeck et al. show that both TTP and HUS are closely related and perhaps a single agent can be used to treat both those abnormalities.

Therefore, claims 6-20 would have been *prima facie* obvious to one of ordinary skill in the art.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Manjunath N. Rao
4/3/02